

Interim Analysis of Prospective, Multi-Center Outcome Observational Cohort Registry of Amniotic Fluid Treatment for Osteoarthritis of the Knee

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Summary

Interim analysis of the first 181 patients in a Registry Study(1)designed for 470 patients suggest that use of a processed amniotic fluid allograft may offer a safe and effective treatment for osteoarthritis (OA) of the knee. Measurements of Mean VAS(2) and WOMAC (3) scoresand subscores showed high statistical significance ($p < 0.005$ or less). Over 75% of patients showed sustained improvement at 90 days.Mean scores for each measure and all patients showedabout 60% improvement compared toTime 0 baseline.The study will continue to evaluate patients through 180 days.

Study Design

Patients with Kellgren Lawrence Grade 1-3 OA via radiologic examination were eligible for enrollment. Excluded patients were < 35 years, had BMI > 45 or had received Hyaluronic Acid (HA) injections in the previous six months, or steroid or platelet rich plasma (PRP) injections in the preceding three months. There were no threshold pain inclusion or exclusion criteria. Eligible patients were injected with 4cc of a minimally processed amniotic fluid tissue product (AmnioVisc™ (4); Liventa Bioscience, West Conshohocken, PA) into the affected knee.Primary study efficacy endpoints are VAS scores and WOMAC Overall Score and WOMAC subscore scales for Pain, Stiffness and Difficulty (function). Theseare measured during office visits at baselineand at 30, 90 and 180 days.

Results

To date, over 420 of the planned 470 Registry enrollees have been treated. This interim analysis shows captured data from the first 181 patients to attain day 30, and 51 patients to attain day 90 follow up.For early and later time points, and all measures, there was a direct inverse correlation of the declining pain scores with the patients' improvements. Different patients had outcomes that were averaged for VAS, overall WOMAC or the separate WOMAC measures. At the follow up visits of 30 and 90 days, patient outcomes improved by Means of $60\% \pm 4\%$ at 30 days compared to Time 0. Percentages of scores or subscores were either maintained or improved through 90 days (Figures1, 2,4).

OMEGA Statistics (Murieta, CA) did Analysis of Variance (ANOVA), and other statistical analyses for all the endpoint measures,to explore the treatment impact at Time 0compared to the measures at 30 daysand 90

Figure 1. Mean VAS Score and Percent Improvement

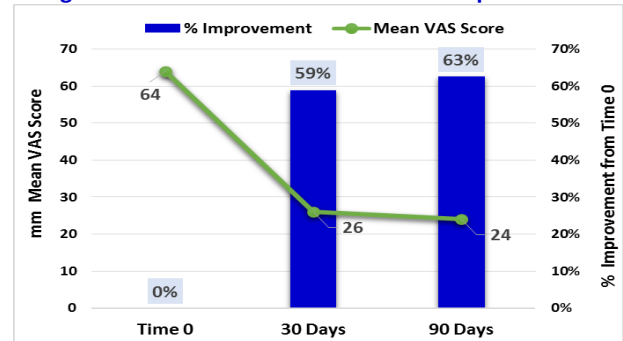
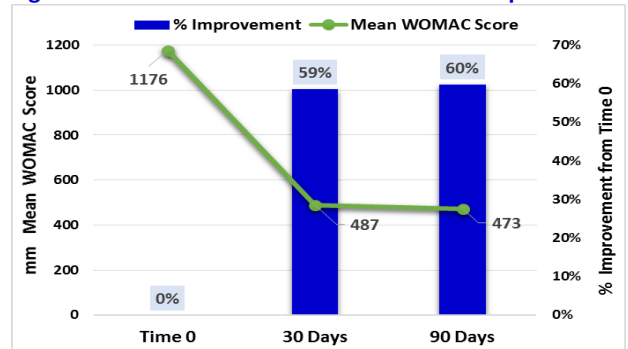


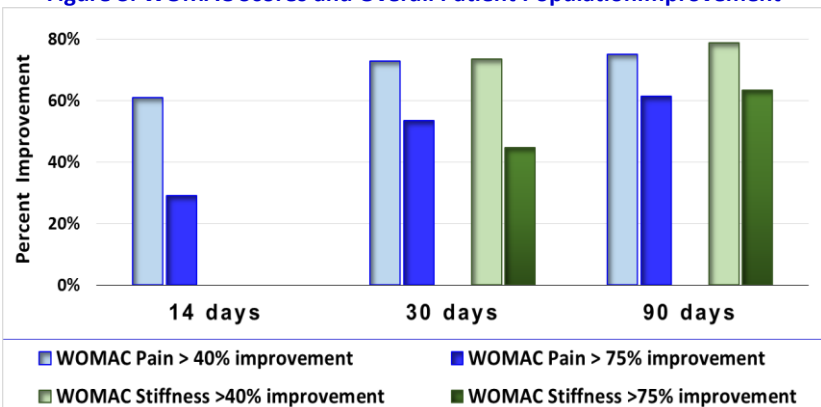
Figure 2. Overall WOMAC Score and Percent Improvement



days. Analyses of within-subjects effects for all endpoints, and across the three time pointsevaluated,showed high statistical significance (p values<0.005 or less) for the mean scores, from t=0 to t=30daysor t=90 days.Measurable improvements were seen by 14 days, with a gradual increase when at least 75% of patients showingimprovementat 90 days (Figure 3).

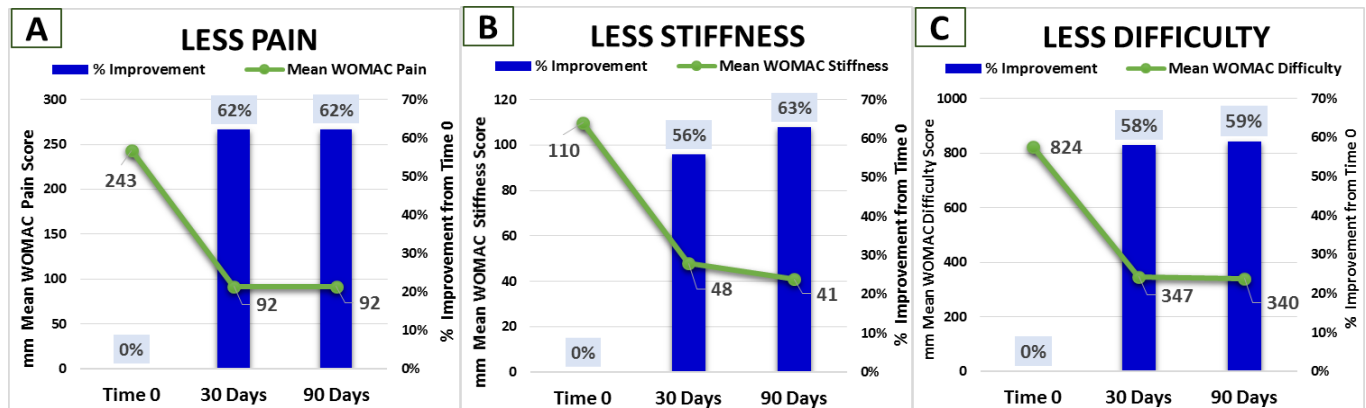
Among181 patients returning for 30 day visits, only 4 treatment-related adverse events (2.2%) were reported.

Figure 3. WOMAC Scores and Overall Patient PopulationImprovement



This was noted as transient pain and tenderness which, “amniosupplementation” may be more durable than single

Figure 4. WOMAC Subscores (Pain, Stiffness, Difficulty) and Percent Patient Improvement



Legend to Figures. Interim analysis data are shown for the first 181 patients to 30 day follow up and the first 51 patients to 90 days follow up visits, with 15 of 23 investigational sites reporting. All endpoints across the three time periods of the study indicated that there was a significant within-subjects effect ($p < 0.005$ or less) for the mean scores, from $t=0$ to $t=30$ Days and to $t=90$ Days.

in all cases, resolved within days with no treatment.

Discussion

Osteoarthritis (OA) of the knee is one of the leading causes of functional limitations and poor quality of life. Nonsurgical treatment of knee OA includes oral medications and injections. The most common injections used to alleviate pain and/or improve function are corticosteroid or hyaluronic acid (HA). However, HA effectiveness has recently been questioned for treating osteoarthritis of the knee in the Medicare population (5) as well as for overall efficacy (6).

Clearly, alternatives are needed to provide pain relief and to improve functional outcomes for this important unmet medical need, which is expected to increase with the aging population. Of importance to physiological and functional outcomes is to improve the lubrication and cushioning of the knee with synthetic or natural products, including allograft tissues.

Allograft amniotic tissues have a long history of clinical use and safety (e.g., 7). The use of amniotic fluid to treat knee OA was initially reported in 1938 by Shimberg (8), who demonstrated that injections of the fluid improved knee function and pain relief without any significant adverse events in 68 patients.

Amniotic fluid is a homolog to synovial fluid which acts as a cushion to protect and lubricate the contents in a closed environment. Important to the use of an allograft tissue product is that the processing to a packaged product is reproducible and meets high quality standards. To that end, this study measured the safety and efficacy of a high quality, processed (9) allograft amniotic fluid to treat osteoarthritic knees using common, validated instruments for product injection and.

The continued or stable improvements that were observed in 75% of the patients through 90 days suggest that

corticosteroid injections or HA treatments, which generally do not show months of patient improvement post-injection.

Although these are very exciting early results from a promising new therapy, additional information is needed for more definitive conclusions. Such data will be obtained upon completion and evaluation of outcomes from this Registry study (10), as well as others that are designed to investigate dosing and injection regimens.

References

1. Registry study approved as a protocol-driven, single arm post-marketing by the Western Institutional Review Board (Olympia, WA).
2. VAS: Visual Analog Scale for Pain Measurement.
3. WOMAC: Western Ontario and McMaster Universities Arthritis Index (WOMAC): a proprietary set of standardized questionnaires used to evaluate patients with osteoarthritis of the knee and other conditions.
4. Product previously named AmnioClear™ LCT.
5. AHRQ Technology Assessment; 11/26/14; Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee.
6. OARSI guidelines for the non-surgical management of knee osteoarthritis; Osteoarthritis Research Society International, May 2013.
7. Trelford JD and Trelford-Sauder M. 1979. The amnion in surgery, past and present. *Am J Obst Gynec* Aug 1, 134(7):833-45.

8. Shimberg M. 1938. The use of amniotic fluid concentrate in orthopedic conditions. J Bone Joint Surgery Am. 20:167-77.
9. cGTP (current Good Tissue Practice) processing done by INCELL Corporation (San Antonio, TX).
10. This Registry is being underwritten by Liventa Bioscience (West Conshohocken, PA).